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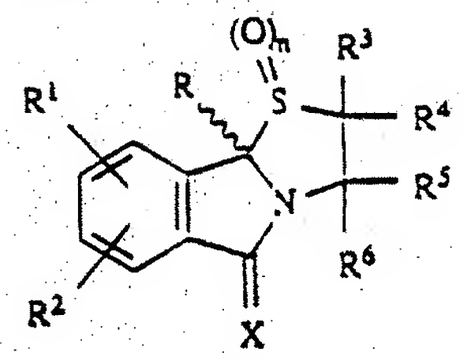
(54) Title: USE OF THIAZOLO-[2,3-A]ISOINDOLE DERIVATIVES AS ANTIVIRAL MEDICAMENTS AND NOVEL THIAZOLO-[2,3-A]ISOINDOLE DERIVATIVES

(54) Bezeichnung: VERWENDUNG VON THIAZOLO-[2,3-A]ISOINDOL-DERIVATEN ALS ANTIVIRALE ARZNEIMITTEL UND NEUE THIAZOLO-[2,3-A]ISOINDOL-DERIVATE

(57) Abstract



(I)

The object of the present invention is the use of thiazolo-[2,3-a]isoindole derivatives for the production of antiviral medicaments and novel thiazolo-[2,3-a]isoindole derivatives. The invention relates in particular to the use of thiazolo-[2,3-a]isoindole derivatives of general formula (I) for the production of medicaments for the treatment of viral or retroviral infections, wherein: X may be an oxygen or sulphur atom, the imino group =NH or an N-C_1-C_5-alkylimino group; n is 0, 1 or 2; R is a hydrogen atom, an aliphatic radical or an optionally substituted carbocyclic or heterocyclic ring; R^1 to R^6 have the meaning given in the description; and their tautomers, enantiomers, diastereomers and physiologically acceptable salts. The present invention also discloses novel thiazolo-[2,3-a]isoindoles of formula (I) in which R is a heterocyclic mono, bi or tricyclic ring.

(57) Zusammenfassung

Gegenstand der vorliegenden Erfindung ist die Verwendung von Thiazolo-[2,3-a]isoindol-Derivaten zur Herstellung von antiviralen Arzneimitteln und neue Thiazolo-[2,3-a] isoindol-Derivate. Die Erfindung betrifft insbesondere die Verwendung von Thiazolo-[2,3-a]isoindol-Derivaten der allgemeinen Formel (I), zur Herstellung von Arzneimitteln zur Behandlung von viralen oder retroviralen Infektionen, wobei X ein Sauerstoff- oder Schwefelatom, die Iminogruppe =NH oder eine N-C_1-C_5-Alkyliminogruppe sein kann, n gleich 0, 1 oder 2 ist, R ein Wasserstoffatom, einen aliphatischen Rest oder einen gegebenenfalls substituierten carbocyclischen oder heterocyclischen Ring bedeutet, R^1 bis R^6 die in der Beschreibung angegebenen Bedeutungen besitzen, sowie deren Tautomere, Enantiomere, Diastereomere und physiologisch verträgliche Salze. Gegenstand der vorliegenden Erfindung sind auch neue Thiazolo[2,3-a]isoindole der Formel (I), in der R einen heterocyclischen mono-, bi- oder tricyclischen Ring bedeutet.

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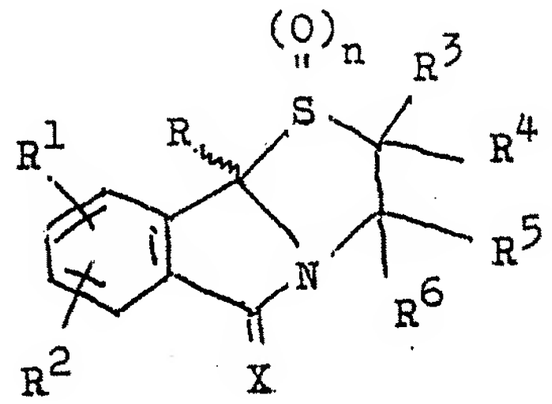
Use of thiazolo-/2,3-a/-isoindole derivatives as anti-viral medicaments and new thiazolo-/2,3-a/-isoindole derivatives

The present invention refers to the use of thiazolo-/2,3-a/-isoindole derivatives for the preparation of anti-viral medicaments and also to new thiazolo-/2,3-a/-isoindole derivatives.

In particular, the invention concerns the use of thiazolo-/2,3-a/-isoindole derivatives of the general formula I



(I),

for the preparation of medicaments for the treatment of viral or retroviral infections, whereby X can be an oxygen or sulphur atom, the imino group =NH or an N-C_1-C_5-alkylimino group, n is equal t o 0, 1 or 2, R signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1-9 C-atoms, which can be substituted by phenyl, or a C_1-C_6-alkoxy-C_1-C_6-alkyl or C_1-C_6-alkylmercapto-C_1-C_6-alkyl radical or signifies a phenyl ring which is possibly substituted one or more times by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_2-C_6-alkenyl,

C_2-C_6-alkynyl, C_2-C_6-alkenyloxy, C_2-C_6-alkenylmercapto, C_2-C_6-alkynyloxy, C_2-C_6-alkynylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, aminocarbonyl, hydroxyl, benzyloxy, phenylmercapto, phenyloxy, nitro, cyano, halogen, trifluoromethyl, azido, formylamino, carboxyl or phenyl or signifies a mono-, bi- or tricyclic carbocyclic ring with 7 - 15 C-atoms or is a heterocyclic mono-, bi- or tricyclic ring system with, in each case, 5 or 6 ring atoms and can contain per ring system 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, and these rings can be substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy, nitro, amino or halogen, R^1 signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 6 C-atoms or C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, carboxyl, halogen, hydroxyl, nitro, cyano, azido, phenyl or benzyloxy, R^2 has the same meaning as R^1, whereby, independently of one another, the radicals R^1 and R^2 can be the same or different, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl,

morpholinocarbonyl, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aryloxycarbonyl, hetaryloxy-carbonyl, aryl-C_1-C_6-alkoxycarbonyl, hetaryl-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxy-C_1-C_6-alkoxycarbonyl or hydroxy-C_1-C_6-alkoxycarbonyl, whereby the aryl and hetaryl radicals can, in each case, be substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy or halogen, R^4, R^5, R^6 have the same meanings as R^3, whereby, independently of one another, R^3, R^4, R^5 and R^6 can be the same or different, as well as their tautomers, enantiomers, diastereomers and physiologically acceptable salts, with the proviso that for the case that R^1, R^2, R^3, R^4, R^5 and R^6 simultaneously signify hydrogen, n signifies the numbers 0 or 1 and X an oxygen atom, R cannot signify hydrogen, an aliphatic group with 1 - 7 C-atoms, which can be substituted by phenyl, or phenyl which is substituted one or more times by C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxyl, trifluoromethyl, methylsulphonyl or halogen.

The subject of the present invention are also new thiazolo-/2,3-a/-isoindoles of the formula I, in which R signifies a heterocyclic mono-, bi- or tricyclic ring with, in each case, 5 or 6 ring atoms and, per ring system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms can be oxygen, sulphur or nitrogen, and these rings can be substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy, nitro, amino or halogen.

Thiazolo-/2,3-a/-isoindoles of the formula I in which X can signify an oxygen atom, n the numbers 0 and 1, R^1 - R^6 in each case hydrogen and R a hydrogen atom or an aliphatic radical with 1 - 7 C-atoms, which can be substituted by phenyl, or R is a phenyl which can be substituted one or more times by alkyl, alkoxy, hydroxyl, trifluoromethyl, methylsulphonyl or halogen, are known from the earlier German Patent Application P 40 35 809.7 as anti-viral medicaments.

Furthermore, individual compounds of the formula I, in which R represents a hydrogen atom, are known from J. Org. Chem. 30, 1965, 1506-1508; J. Am. Chem. Soc. 80, 1958, 702-707 and Liebigs Ann. Chem., 4, 1985, 657-672. Compounds with X = O and R = phenyl or naphthyl radical are described in GB 1,039,117 as medicaments with anti-inflammatory, anti-convulsive and analgesic action.

The task forming the basis of the present invention is to find a further medical indication for known compounds of the formula I and to make available new thiazolo-/2,3-a/-isoindoles with anti-viral effectiveness. This task is solved by the features characterised in the claims.

The compounds of the formula I display valuable pharmacological properties. In particular, they are suitable for the therapy and prophylaxis of infections which are caused by DNA viruses, such as e.g. the herpes simplex virus, the cytomegalovirus, Papilloma-

viruses, the varicella-zoster virus or Epstein-Barr virus, or RNS viruses, such as togaviruses, or especially retroviruses, such as the oncoviruses HTLV-I and II, as well as the lentiviruses visna and human immune deficiency virus HIV-1 and 2.

The compounds of the formula I appear to be especially suitable for the treatment of the clinical manifestations of the retroviral HIV infection in humans, such as the persistent generalised lymph-adenopathy (PGL), the advance stage of the AIDS-related complex (ARC) and the clinical complete picture of AIDS.

The compounds of the general formula I according to the invention possess an outstanding anti-viral action and are especially suitable for the treatment of viral and retroviral infections, respectively. Viral infections of mammals, especially of humans, are very widespread. In spite of intensive efforts, hitherto it has not been possible to make available chemotherapeutics which interfere causally or symptomatically with the virally or retrovirally caused appearances of disease with a recognisable substantially success. At present, it is not possible to cure certain viral diseases, such as for example the acquired immune deficiency syndrome (AIDS), the AIDS-related complex (ARC) and their preliminary stages, herpes, cytomegalovirus (CMV), influenza and other virus infections, or chemotherapeutically

favourably to influence their symptoms. At present, for example, for the treatment of AIDS there is available almost exclusively 3'-azido-3'-deoxythymidine (AZT), known as Zidovudine or Retrovir R. However, AZT is characterised by a very narrow therapeutic range or by very severe toxicities already appearing in the therapeutic range (Hirsch, M.S. (1988) J. Infec. Dis., 157, 427-431). The compounds of the formula I do not possess these disadvantages. They act anti-virally without being cytotoxic in the pharmacologically relevant doses.

It could now be demonstrated that compounds of the general formula I inhibit the multiplication of DNA or RNA viruses, respectively, at the stage of the virus-specific DNA or RNA transcription, respectively. Via the inhibition of the enzyme reverse transcriptase, the substances can influence the multiplication of retroviruses (cf. Proc. Natl. Acad. Sci. USA, 83, 1911, 1986 and Nature, 325, 773, 1987, respectively).

Since a very great need exists for chemotherapeutics which interfere as specifically as possible with retrovirally-caused diseases or their symptoms without influencing the normally occurring natural body functions, the said compounds could be advantageously used prophylactically or therapeutically in the treatment of diseases in which a retroviral infection is of pathophysiological,

symptomatic or clinical relevance.

The compounds of the formula I possess a chirality centre and can be used not only in the form of their racemates but also in the form of their enantiomers and diastereomers. The separation of the racemates into enantiomers can be carried out analytically, semi-preparatively and preparatively by chromatography on suitable optically-active phases with conventional elution agents. As optically-active phases there are suitable, for example, optically-active polyacrylamides or polymethacrylamides, in some cases also on silica gel (e.g. ChiraSpher® of Merck, Chiralpak® OT/OP of Baker), cellulose esters/carbamates (e.g. Chiracel® OB/OY of Baker/daicel), phases based on cyclodextrin or crown ethers (e.g. Crownpak® of Daicel) or microcrystalline cellulose triacetate (Merck).

An aliphatic radical signifies a straight-chained or branched alkyl, alkenyl or alkynyl radical with 1 - 9, preferably 2 - 7 carbon atoms, such as e.g. the propyl, isopropyl, butyl, isobutyl, pentyl, hexyl or heptyl radical. As unsaturated radicals, there come into question C_2-C_7-alkenyl and alkynyl radicals, preferably C_2-C_5, such as e.g. the allyl, dimethylallyl, butenyl, isobutenyl, pentenyl or propynyl radical.

An aliphatic radical which can be substituted by phenyl is especially a phenyl-C_1-C_6-alkyl group, such

as e.g. the benzyl, phenethyl, phenylpropyl or phenylbutyl radical.

If R signifies a phenyl ring, this can be substituted one, two or three times. Independently of one another, the substituents can stand in the o-, m- or p-position.

A carbocyclic ring with 7 - 15 C-atoms can be mono-, bi- or tricyclic and, in each case, have 5 or 6 C-atoms per ring. This ring can be saturated, unsaturated, partly saturated or aromatic. By way of example, there may be mentioned the following ring systems: the naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, indanyl, acenaphthylenyl, norbornyl, adamantyl ring or a C_3-C_7-cycloalkyl or C_5-C_8-cycloalkenyl group, whereby, in the last two cases, the corresponding five- or six-membered rings are preferred.

The heretocyclic mono-, bi- or tricyclic ring systems contain 5 or 6 carbon atoms per ring system, whereby 1 - 4 or 1 - 5 carbon atoms, respectively, can be replaced by the heteroatoms oxygen, sulphur and/or nitrogen. The ring systems can be aromatic, partly or completely hydrogenated. By way of example, the following ring systems may be mentioned: the pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrrole, pyrazole, imidazole, triazole, thiazole, oxazole, isoxazole, oxadiazole, furazane, furan, thiophene, indole, quinoline, isoquinoline, cumarone, thionaphthene, benzoxazole, benzthiazole, indazole,

benzimidazole, benzthiazole, chromene, phthalazine, quinazoline, quinoxaline, methylenedioxybenzene, carbazole, acridine, phenoxazine, phenothiazine, phenazine or purine system, whereby the unsaturated or aromatic carbo- and heterocycles can be partly or completely hydrogenated.

As aryl or hetaryl radicals, respectively, in the definition of R^3 - R^6, the phenyl, naphthyl or pyridyl radical comes into question, whereby, in particular, these radicals can be substituted once or twice by C_1-C_3-alkyl, C_1-C_3-alkoxy or halogen.

R preferably signifies unsubstituted phenyl or phenyl substituted once or twice by C_1-C_3-alkyl, C_1-C_3-alkoxy, C_1-C_3-alkylmercapto, C_1-C_3-alkylsulphinyl, C_1-C_3-alkylsulphonyl, C_2-C_4-alkenyl, C_2-C_3-alkynyl, C_3-C_4-alkenyloxy, C_1-C_3-alkylamino, C_1-C_3-dialkylamino, C_1-C_3-alkylcarbonylamino, C_1-C_3-alkylaminocarbonyl, C_1-C_3-alkoxycarbonyl, amino, hydroxyl, nitro, azido, trifluoromethyl, cyano or halogen.

Carbocyclic rings are preferably biphenyl, naphthyl, anthracenyl, indanyl, fluorenyl, acenaphthenyl, phenanthrenyl, norbornyl, adamantyl, C_3-C_6-cycloalkyl, C_5-C_8-cycloalkenyl. Heterocyclic ring systems are preferably pyrrole, imidazole, furan, thiophene, pyridine, pyrimidine, thiazole, triazine, indole, quinoline, isoquinoline, cumarone, thionaphthene, benzimidazole, quinazoline, methylenedioxybenzene, ethylenedioxybenzene, carbazole,

acridine and phenothiazine.

For the radicals R^1 and R^2 are preferred hydrogen, C_1-C_3-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_3-alkoxy, C_1-C_3-alkylmercapto, C_1-C_3-alkylamino, C_1-C_3-alkoxycarbonyl, sulphonamide, amino, halogen, hydroxyl, cyano and azido, whereby these radicals stand especially in the 7-, 8- or 9-position of the thiazolo-[2,3-a]-isoindole ring.

Preferred substituents for R^3, R^4, R^5 and R^6 are hydrogen, C_1-C_3-alkyl, C_1-C_3-alkoxy, C_1-C_3-alkyl-mercapto, carboxyl, C_1-C_3-alkoxycarbonyl, morpholino-carbonyl, aminocarbonyl, C_1-C_3-alkylaminocarbonyl, di-C_1-C_3-alkylaminocarbonyl, C_1-C_3-alkoxy-C_1-C_3-alkoxycarbonyl, pyridyl-C_1-C_3-alkoxycarbonyl, halogen, cyano and hydroxyl, whereby R^3 and R^4 especially signify hydrogen. The radicals R^3 - R^6 can be the same or different but those derivatives are preferred in which at least two, preferably three of these radicals signify hydrogen.

X is preferably oxygen or sulphur, n is preferably equal to 0. By halogen is generally to be understood fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine.

Especially preferred radicals for R are C_3-C_5-alkyl, C_2-C_5-alkenyl, C_2-C_4-alkynyl, benzyl, phenethyl; phenyl; phenyl mono- or disubstituted by C_1-C_3-alkyl, C_1-C_3-alkoxy, C_1-C_3-alkylmercapto, allyl, allyloxy, C_1-C_3-alkylamino, di-C_1-C_3-alkyl-

amino, amino, hydroxyl, azido, nitro, trifluoromethyl, cyano or halogen and phenyl trisubstituted by methyl or halogen; naphthyl, anthracenyl, indanyl, acenaphthenyl, phenanthrenyl, adamantyl, cyclohexyl, cyclohexenyl, furyl, thienyl, pyridyl, pyrimidinyl, thiazolyl, indolyl, quinolinyl, benzimidazolyll, methylenedioxyphenyl, carbazolyl and phenothiazinyl.

For R^1 and R^2, independently of one another, are especially preferred hydrogen, methyl, ethyl, isopropyl, allyl, methoxy, ethoxy, methylmercapto, ethylmercapto, methylamino, methoxycarbonyl, ethoxycarbonyl, amino, azido, cyano, hydroxyl and halogen, whereby halogen especially signifies chlorine and bromine.

For R^3, R^4, R^5 and R^6 are especially preferred methyl, ethyl, isopropyl, methoxy, ethoxy, methylmercapto, ethylmercapto, methylamino, amino, chlorine, bromine and cyano.

Especially preferred are compounds of the general formula I in which R, R^1, X and n have the above-given meaning and R^2, R^3, R^4, R^5 and R^6 are hydrogen, methyl, ethyl, chlorine, bromine, methoxy or ethoxy, whereby the radicals R^2 to R^6 preferably represent hydrogen.

The new compounds of the formula I in which R signifies a heterocyclic radical are especially those derivatives in which R signifies thienyl, furyl, pyridyl, thionaphthenyl or indolyl, whereby these radicals can be especially substituted by C_1-C_6-alkyl and halogen.

The medicaments containing at least one compound of the formula I for the treatment of viral infections can be administered enterally or parenterally in liquid or solid form. There hereby come into question the usual forms of administration, such as for example tablets, capsules, dragees, syrups, solutions or susp ensions. As injection medium, water is preferably used which contains the additives usual in the case of injection solutions, such as stabilising agents, solubilising agents and buffers. Such additives are e.g. tartrate and citrate buffers, ethanol, complex formers, such as ethylenediamine-tetraacetic acid and its non-toxic salts, high molecular polymers, such as liquid polyethylene oxide, for viscosity regulation. Liquid carrier materials for injection solutions must be sterile and are preferably filled into ampoules. Solid carrier materials are, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular fatty acids, such as stearic acid, gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high molecular polymers, such as polyethylene glycols etc. Compositions which are suitable for oral administration can, if desired, contain flavouring and sweetening agents.

The medicaments containing at least one compound of the formula I are prepared in that one mixes a compound of the formula I with usual pharmaceutical

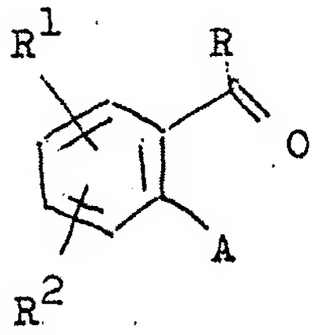
adjuvants and works up to medicinal forms, such as e.g. tablets, dragees, capsules or solutions. These medicinal forms are confectioned to packaging units ready for sale and provided with an appropriate instruction, e.g. in the form of a packaging leaflet, from which follows the use for the treatment of viral or retroviral infections or of virally- or retrovirally-caused diseases.

The dosaging can depend upon various factors, such as mode of administration, species, age or individual state of health. The compounds according to the invention are usually administered in amounts of 0.1 - 100 mg, preferably of 0.2 - 80 mg per day and per kg of body weight. It is preferred to divide up the daily dose into 2 - 5 administrations, whereby, in the case of each administration, 1 - 2 tablets with an active material content of 0.5 - 500 mg are given. The tablets can also be retarded, whereby the number of administrations is reduced to 1 - 3. The active material content of the retarded tablets can amount to 2 - 1000 mg. The active material can also be given by continuous infusion, whereby the amounts of 5 - 1000 mg per day normally suffice.

The compounds of the formula I can also be used in the form of their physiologicelly acceptable salts, such as e.g. the alkali metal or alkaline earth metal salts, insofar as these compounds possess acid groups, such as e.g. a free carboxyl group. If basic groups

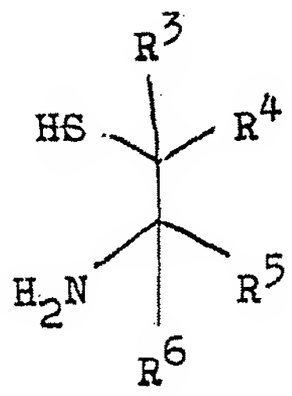
are present, then the compounds of the formula I can be converted into the corresponding physiologically acceptable acid-addition salts with the help of organic or inorganic acids.

The compounds of the general formula I according to the invention can be prepared by processes known from the literature in that one reacts possibly substituted benzoic acid derivatives of the general formula II



(II)

in which R, R^1 and R^2 have the above-given meaning and A is equal to -COOH or C=N, with substituted or unsubstituted cysteamine of the general formula III



(III)

in which R^3, R^4, R^5 and R^6 have the above-given meaning, in a suitable inert solvent at room temperature to reflux temperature, possibly in the presence of catalytic amounts of acid, e.g. p-toluenesulphonic acid, and possibly subsequently converts compounds obtained of the formula I into

other compounds of the formula I and subsequently purifies chromatographically or by recrystallisation. Racemates can be separated into the antipodes by chromatography on suitable optically-active phases, e.g. cellulose triacetate.

The subsequent conversions of compounds of the formula I into other compounds of the formula I concerns the preparation of thiazolo-/2,3-a/-isoindole derivatives with X = S or N-alkylimine.

Compounds with X = S are prepared by reaction of compounds of the formula I, in which X signifies an oxygen atom, with sulphur group-transferring compounds, such as e.g. Lawesson's reagent. Compounds with X = N-alkylimino are prepared by reaction of the corresponding imino compounds of the general formula I with alkylamines according to per se known methods.

The benzoic acid derivatives of the general formula I are also known from the literature and are prepared e.g. by Friedel-Crafts acylation of substituted or unsubstituted phthalic anhydride with possibly substituted arenes in the presence of a Lewis acid (e.g. aluminium chloride) or by reaction of Grignard reagents of the general formula IV

R-MgBr (IV),

in which R has the above-given meaning with the

exception of hydrogen, with phthalic acid anhydride which is possibly substituted, in suitable inert solvents at low temperatures.

The processes for the preparation of the compounds of the general formula I according to the invention can also be taken from the patent applications and literature references mentioned in the prior art (cf. U.S. Patent 3,334,113, CH-469,733, Belgian Patent Application 659,528 or U.S. Patent 3,646,022, U.S. 2,860,985, Belgian Patent Application 564,592, J. Org. Chem., 30, 1506 (1965), as well as J. Org. Chem., 34, 165 (1969).

In the meaning of the present invention, apart from the compounds mentioned in the Examples and those obtained by combination of all meanings of the substituents mentioned in the claims, the following compounds of the formula I come into question which can be present as racemic mixtures or in optically-active form or as pure R- and S-enantiomers, respectively:

1. 8,9b-dimethyl-2,3-dihydrothiazolo-/2,3-a7-iso-indol-5(9bH)-one
2. 8-chloro-9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
3. 8-fluoro-9b-(4-methylphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
4. 8-chloro-9b-(3-methylphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
5. 3-methyl-9b-(4-ethylphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
6. 9b-(2,3-dimethylphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-thione
7. 8-chloro-9b-(3,4-dimethylphenyl)-2,3-dihydro-thiazolo-/2,3-a7-isoindol-5(9bH)-thione
8. 2-ethyl-9b-(2,5-dimethylphenyl)-2,3-dihydro-thiazolo-/2,3-a7-isoindol-5(9bH)-one
9. 8-chloro-9b-(3-trifluoromethylphenyl)-2,3-dihydro-thiazolo-/2,3-a7-isoindol-5(9bH)-one
10. 6-methoxy-9b-(4-trifluoromethylphenyl)-2,3-dihydro-thiazolo-/2,3-a7-isoindol-5(9bH)-one
11. 9b-(4-hydroxyphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindole-5(9bH)-thione
12. 8-chloro-9b-(3-hydroxyphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
13. 7-methylmercapto-9b-(4-ethoxyphenyl)-2,3-dihydro-thiazolo-/2,3-a7-isoindol-5(9bH)-one
14. 9-methyl-9b-(3-methoxyphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bE)-one

15. 8-fluoro-9b-(3-fluorophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
16. 9b-(4-chlorophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-thione
17. 8-methyl-9b-(3-methylsulphonylphenyl)-2,3-dihydro-thiazolo-/2,3-a7-isoindol-5(9bH)-one
18. 8-chloro-9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one 1-oxide
19. 8-chloro-9b-benzyl-2,3-dihydrothiazaolo-/2,3-a7-isoindol-5(9bH)-one
20. 2,2-dimethyl-9b-phenethyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
21. 9b-(3-methylmercaptophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
22. 9b-(3-methylaminophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
23. 9b-(3-azidophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
24. 8-methyl-9b-allyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
25. 8-chloro-9b-(3,5-dimethylphenyl)-2,3-dihydro-thiazolo-/2,3-a7-isoindol-5(9bH)-one
26. 8-methyl-9b-(1-naphthyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
27. 9b-(anthracen-1-yl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one
28. 9b-(anthracen-9-yl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one

29. 9b-(inden-1-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one
30. 9b-(inden-3-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one
31. 9b-(inden-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindole-5(9bH)-thione
32. 9b-(phenanthren-1-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one
33. 9b-(phenanthren-9-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one
34. 9b-(cyclohexen-3-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindole-5(9bH)-thione
35. 9b-(2-furyl)-2,3-dihydrothiazolo-[2,3-a]-isoindole-5(9bH)-thione
36. 9b-(3-furyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one
37. 9b-(2-thienyl)-2,3-dihydrothiazolo-[2,3-a]-isoindole-5(9bH)-thione
38. 9b-(3-thienyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one
39. 9b-(pyrimidin-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one
40. 9b-(thiazol-2-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one
41. 9b-(thiazol-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindole-5(9bH)-thione
42. 9b-(indol-3-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

43. 9b-(indol-7-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

44. 9b-(quinolin-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

45. 9b-(quinolin-5-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5-(9bH)-thione

46. 9b-(benzimidazol-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5-(9bH)-one

47. 9b-(carbazol-1-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

48. 9b-(carbazol-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindole-5(9bH)-thione

49. 9b-(phenothiazin-1-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindole-5(9bH)-thione

50. 9b-(phenothiazin-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

51. 9b-(4-quinazolin-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

52. 8-chloro-9b-(inden-3-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

53. 8-methyl-9b-(isoquinolin-1-yl)-2,3-dihydro-thiazolo-[2,3-a]-isoindole-5(9bH)-thione

54. 9-methoxy-9b-(1-naphthyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

55. 9b-(cumaron-3-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

56. 9b-(1-naphthyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one 1,1-dioxide

57. 9b-(1-naphthyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one 1-oxide.

Example 1.

9b-(1-Naphthyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one.

2.76 g (10 mmol) 2-(1-naphthoyl)-benzoic acid were dissolved in 100 ml xylene and, after addition of 1.54 g (20 mmol) cysteamine, as well as of a catalytic amount of p-toluenesulphonic acid, heated under reflux for 1 h on a water separator. The solvent was then removed in a vacuum and the residue recrystallised from ethanol. Yield 1.54 g (67% of theory); m.p. 151-152°C.

The 2-(1-naphthoyl)-benzoic acid used was prepared by slow dropwise addition of 1-naphthyl magnesium bromide in ether/toluene at -10°C to a solution of phthalic acid anhydride in toluene, after 2 hours post-stirring, addition of sat. NH_4Cl solution, extraction with ethyl acetate, shaking out of the ethyl acetate phase with 2N soda solution and renewed extraction of the acidified soda phase with ethyl acetate. Yield after recrystallisation from ethanol 64% of theory; m.p. 170°C.

The following compounds were prepared analogously to Example 1:

1.1 9b-(2-naphthyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; amorphous; R_f = 0.5 (ethyl acetate/isohexane 1/3) from 2-(2-naphthoyl)-benzoic acid

and cysteamine (66% yield)

1.2 9b-(anthracen-9-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 198°C, from 2-(9-anthracenoyl)-benzoic acid and cysteamine (44% yield)

1.3 7-chloro-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 123°C, from 5-chloro-2-benzoylbenzoic acid and cysteamine (61% yield)

1.4 7-methyl-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 98°C, from 5-methyl-2-benzoylbenzoic acid and cysteamine (59% yield)

1.5 6-methyl-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 185°C, from 6-methyl-2-benzoylbenzoic acid and cysteamine (79% yield)

1.6 7-methoxy-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; R_f = 0.33 (ethyl acetate/isohexane 1/3) from 5-methoxy-2-benzoylbenzoic acid and cysteamine (55% yield)

1.7 7,8-dichloro-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 112-114°C, from 4,5-dichloro-2-benzoylbenzoic acid and cysteamine (67% yield)

1.8 9b-(2-thienyl)-2,3-dihydrothiazolo-[2,3-a]-iso-indol-5(9bH)-one; m.p. 151°C (ethanol/H_2O) from 2-(2-thienoyl)-benzoic acid and cysteamine (63% yield)

1.9 9b-(2-furyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 114°C (ethanol/ether) from 2-(2-furoyl)-benzoic acid and cysteamine (70% yield)

1.10 9b-cyclopentyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; oil; R_f = 0.85 (CH_2Cl_2/CH_3OH 9/1) from 2-cyclopentoylbenzoic acid and cysteamine (81% yield). The purification of this compound takes place by column chromatography with ethyl acetate/isohexane 1/1

1.11 8-chloro-7-sulphonamido-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 245-246°C, from 4-chloro-5-sulphonamido-2-benzoyl-benzoic acid and cysteamine (54% yield)

1.12 8-chloro-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 113-136°C, from 4-chloro-2-benzoylbenzoic acid and cysteamine (68% yield)

1.13 8-methyl-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 115-118°C, from 4-methyl-2-benzoylbenzoic acid and cysteamine (75% yield)

1.14 9b-(4-pyridyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 114°C, from 2-(4-pyridoyl)-benzoic acid and cysteamine (68% yield)

1.15 9b-(2-pyridyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 115-116°C, from 2-(2-pyridoyl)-benzoic acid and cysteamine (61% yield)

1.16 9b-(3-pyridyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 149-152°C, from 2-(3-pyridoyl)-benzoic acid and cysteamine (57% yield)

1.17 9b-cyclohexyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; oil; R_f = 0.55 (ethyl acetate/isohexane 1/3); from 2-cyclohexoylbenzoic acid and cysteamine (79% yield)

1.18 9b-(2-aminophenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 147-151°C (isopropanol), from 2-(2-aminobenzoyl)-benzoic acid and cysteamine (43% yield)

1.19 9b-(4-aminophenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 179-185°C (isopropanol), from 2-(4-aminobenzoyl)-benzoic acid and cysteamine (49% yield)

1.20 9b-(indan-4-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 151-153°C, from 2-(indan-4-ylcarbonyl)-benzoic acid and cysteamine (63% yield)

1.21 9b-(2-nitro-5-methylphenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 161-164°C (ethyl acetate/isohexane), from 2-(2-nitro-5-methylbenzoyl)-benzoic acid and cysteamine (70% yield)

1.22 8-methoxy-9b-phenyl-2,3-dihydrothiazolo[2,3-a]-isoindol-5(9bH)-one; oil; from 4-methoxybenzoyl-benzoic acid and cysteamine (56% yield)

1.23 9b-(3-nitrophenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 91-97°C, from 2-(3-nitrobenzoyl)-benzoic acid and cysteamine (33% yield)

1.24 8-chloro-9b-1-(naphthyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 156-159°C (methanol), from 4-chloro-2-(1-naphthoyl)-benzoic acid and cysteamine (28% yield)

1.25 9b-(3-dimethylaminophenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 149-151°C (methanol), from 2-(3-dimethylaminobenzoyl)-benzoic acid and cysteamine (27% yield)

1.26 9b-(9-phenanthrenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 170-172°C (ethyl acetate/isohexane), from 2-(9-phenanthrenoyl)-benzoic acid and cysteamine (64% yield)

1.27 9b-(3-amino-4-chlorophenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 180°C (isopropanol), from 2-(3-amino-4-chlorobenzoyl)-benzoic acid and cysteamine (41% yield)

1.28 9b-(5-fluoro-1-naphthyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 157°C, from 2-(5-fluoro-1-naphthoyl)-benzoic acid and cysteamine (85% yield)

1.29 8-chloro-9b-(3-chlorophenyl)-2,3-dihydrothiazolo-[2,3-a]-one, m.p. 162°C, from 4-chloro-2-(3-chlorobenzoyl)-benzoic acid and cysteamine (73% yield)

1.30 6-methoxy-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 187°C (isopropanol), from 6-methoxy-2-benzoylbenzoic acid and cysteamine (42% yield)

1.31 8-chloro-9b-(3-methylphenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 129-132°C (ether), from 4-chloro-2-(3-methylbenzoyl)-benzoic acid and cysteamine (24% yield)

1.32 7-chloro-9b-(3-methylphenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 76-80°C (ether), from 5-chloro-2-(3-methylbenzoyl)-benzoic acid and cysteamine (27% yield)

1.33 9b-(4-methylpyridin-2-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; oil; from 2-[2-(4-methylpyridoyl)]-benzoic acid and cysteamine (53% yield)

1.34 9b-(2-thionaphthenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5-(9bH)-one; m.p. 130-133°C, from 2-(2-thionaphthenoyl)-benzoic acid and cysteamine (62% yield)

1.35 9b-(3-thionaphthenyl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 206-216°C, from 2-(3-thionaphthenoyl)-benzoic acid and cysteamine (50% yield)

1.36 9b-(indol-3-yl)-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 272-275°C (methanol), from 2-(indol-3-ylcarbonyl)-benzoic acid and cysteamine (42% yield).

The compounds were, in each case, recrystallised from ethanol insofar as nothing otherwise is stated.

Example 2

9b-Phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindole-5(9bH)-thione.

2 g (7.5 mmol) 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one /J. Org. Chem., 34, 165 (1969)7 in 100 ml abs. dioxane were mixed with 3.8 g (9.4 mmol) Lawesson's reagent /2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulphide7 and stirred for 5 h at 60°C (TLC control).

After cooling, it was filtered off from precipitate, the filtrate evaporated in a vacuum and the residue purified by flash column chromatography with heptane/methyl ethyl ketone 6/1 as eluent. Yield 1.24 g (58% of theory); m.p. 152-155°C.

There was prepared analogously:

2.1 9b-(1-naphthyl)-2,3-dihydrothiazolo-/2,3-a7-isoindole-5(9bH)-thione

was prepared from the corresponding oxo compound (Example 1). Yield 71% of theory; m.p. °C.

Example 3

Enantiomer separation of rac-9b-(1-naphthyl)-2,3-dihydrothiazolo-/2,3-a7-isoindole-5(9bH)-one on cellulose triacetate

For the separation of the antipodes, 200 mg of the racemate were dissolved in 15 ml methanol, applied to a column with 50 mm inner diameter and

300 mm length (corresponding to 250 g cellulose triacetate, 15-25 µ grain size, Merck 16326) and eluted with methanol (flow 7.5 ml/min, about 1.5 bar).

	Peak I	Peak II
UV detection [nm]:	254	254
run time [min]:	110	255
$[\alpha]_D^{20+}$	-454° +/- 5	454 +/- 5
m.p. [°C]	175-176	175-176
abs. configuration	(S)	(R)

The enantiomers were recrystallised from methanol.

+ enantiomer purity according to HPLC in each case

> 99.6% ee

Analogously to Example 3 were separated:

3.1 (-)-8-chloro-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

(m.p. 87-93°C)

3.2 (+)-8-chloro-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one

(m.p. 87-93°C); with ethanol as eluent

3.3 (-)-8-chloro-9b-(3-chlorophenyl)-2,3-dihydro-thiazolo-[2,3-a]-isoindol-5(9bH)-one

(m.p. 138°C/ethanol; $_D$ = -236°C/c = 1/$CHCl_3$)

3.4 (+)-8-chloro-9b-(3-chlorophenyl)-2,3-dihydro-thiazolo-[2,3-a]-5(9bH)-one;

(m.p. 138°C/ethanol; $_D$ = +236°C/c = 1/$CHCl_3$ with methanol as eluent.

Example 4

9b-(4-Azidophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one

2.1 g (7.4 mmol) 9b-(4-aminophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one were suspended in 12 ml 2N HCl, mixed at 0 - 5°C within 15 min with a solution of 0.55 g (8 mmol) $NaNO_2$ in 3 ml H_2O and stirred for 30 min at 0°C.

A solution of 0.6 g (9.2 mmol) NaN_3 in 8 ml H_2O was then added dropwise thereto within 10 min, after-stirred for 30 min and the resultant precipitate filtered off w ith suction. The crude product was purified by column chromatography on silica gel 60 with ether/isohexane 1/2 as eluent. Yield 1.62 g (71% of theory); m.p.. > 140°C decomp.

4.1 9b-(3-azidophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one

was prepared analogously to Example 4 from 9b-(3-aminophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one in 86% yield. M.p. 100-101°C (recrystallisation from ether).

Example 5

9b-(3-Aminophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one

11.2 g (35.7 mmol) 9b-(3-nitrophenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one in 90 ml ethanol were mixed at the boiling point with 23 g $Na_2S_2O_4$ in 90 ml H_2O within 5 min and heated

under reflux for 1 h.

The ethanol was then evaporated off in a vacuum, the aqueous phase extracted several times with dichloromethane and the organic phase dried over Na_2SO_4. After removal of the solvent on a rotary evaporator, the residue was recrystallised from dichloromethane. Yield 6.02 g (60% of theory); m.p. 184-186°C.

5.1 9b-(2-amino-5-methylphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one

was prepared analogously to Example 5 from 9b-(2-nitro-5-methylphenyl)-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one in 53% yield. M.p. 153-156°C (recrystallisation from dichloromethane).

Example 6

9b-Phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid methyl ester

1.7 g (9.9 mmol) L-cysteine methyl ester hydrochloride and 1.35 g sodium acetate were introduced portionwise at 100°C over a period of time of 10 h into a solution of 1 g (4.4 mmol) 2-benzoylbenzoic acid in 10 ml xylene. After a further 3 h at 100°C, the xylene was distilled off, the residue taken up in dichloromethane and washed with $NaHCO_3$ solution, as well as water. The ester was isolated by removal of the solvent and used without further purification in the next reaction; $[\alpha]_D$ = -57°C/c = 1/MeOH).

Example 7

9b-Phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid

The crude product of the last reaction was dissolved in 5 ml ethanol, mixed with 2 ml 2N NaOH and stirred for 2 h at 40°C.

The ethanol was then distilled off, the aqueous phase acidified with 6N HCl and the free acid filtered off with suction. Yield 0.6 g (44% of theory, referred to the 2-benzoylbenzoic acid used); m.p. 98-98°C (recrystallisation from ethanol). $[\alpha]_D$ = -211°/c = 0.89/MeOH.

Example 8

9b-Phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid morpholide

311 mg (1 mmol) 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid (Example 7) in 10 ml abs. dichloromethane were mixed at -15°C with 101 mg (1 mmol) 4-methylmorpholine and subsequently with 155 mg (1.1 mmol) isobutyl chloroformate and stirred for 15 min. 96 mg (1.1 mmol) morpholine were then added thereto, warmed to RT and stirred for 4 h at RT. After addition of a further 20 ml dichloromethane, the solution was shaken out with $NaHCO_3$ solution and water, dried over Na_2SO_4 and freed from solvent. The residue was purified by chromatography on silica gel with ethyl acetate as eluent. Yield 158 mg (51% of theory); m.p. 138-141°C.

8.1 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid amide

was prepared analogously to Example 8 in 57% yield, m.p. 164°C (ethyl acetate).

8.2 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid methylamide

was prepared analogously to Example 8 in 41% yield, m.p. 160-162°C (ethyl acetate)

8.3 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid dimethylamide

was prepared analogously to Example 8 in 59% yield, m.p. 178°C (ethyl acetate)

8.4 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid propyl ester

was prepared analogously to Example 8 by reaction of the active ester with n-propanol in 27% yield, m.p. 103-106°C

8.5 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid isopropyl ester

was prepared analogously to Example 8 by reaction of the active ester with 2-propanol in 31% yield, m.p. 88-90°C

8.6 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid methoxyethyl ester

was prepared analogously to Example 8 by reaction of the active ester with 2-methoxyethanol in 30% yield, oil

8.7 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid isobutyl ester
was prepared analogously to Example 8 by reaction of the active ester with 2-methyl-1-propanol in 42% yield, oil

8.8 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid 2-pyridylmethyl ester
was prepared analogously to Example 8 by reaction of the active ester with 2-(hydroxymethyl)-pyridine in 42% yield

8.9 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid (3-pyridylmethyl)-ester
was prepared analogously to Example 8 by reaction of the active ester with 3-(hydroxymethyl)-pyridine in 60% yield, m.p. 119-121°C

8.10 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one-3-carboxylic acid (4-pyridylmethyl)-ester
was prepared analogously to Example 8 by reaction of the active ester with 4-(hydroxymethyl)-pyridine in 37% yield, m.p. 125-128°C.

Example 9

Inhibition of reverse transcriptase (RT) by derivatives of 9b-phenyl-2,3-dihydrothiazolo-/2,3-a7-isoindol-5(9bH)-one.

The screening test system contains the purified RT from HIV-1, which was expressed by gene technological methods in E. coli, as well as the components of the initiation complex, such as the in vitro transcripts of the HIV-LTR's with the neighbouring primer

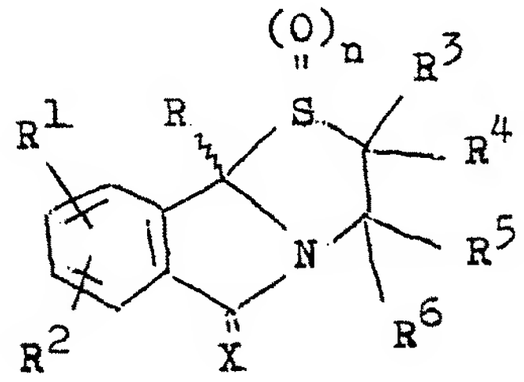
binding site as template and an 18mer oligonucleotide complementary to the primer binding site as primer. The [^{3}H]-thymidine-5'-triphosphate incorporation was measured by counting in a β-counter. In the following Table, there is given the IC_{50} value for the compounds investigated. This value corresponds to that concentration of the test compounds which brings about an inhibition of the reverse transcriptase activity by 50%. As comparative substance, there was correspondingly determined the value for AZT.

Results:

substance	inhibition of the HIV-RT IC_{50} [M]
3'-azido-3'-desoxythymidine-5'-triphosphate [AZT-TP]	6.0×10^{-6}
9b-phenyl-2,3-dihydro-thiazolo-[2,3-a]-isoindole-5(9bH)-thione	3.5×10^{-6}
7,8-dichloro-9b-phenyl-2,3-dihydrothiazolo-[2,3-a]-isoindol-5(9bH)-one	4.5×10^{-6}
9b-(2-thienyl)-2,3-dihydro-thiazolo-[2,3-a]-isoindol-5(9bH)-one	2.7×10^{-6}
9b-(2-furyl)-2,3-dihydro-thiazolo-[2,3-a]-isoindol-5(9bH)-one	1.4×10^{-6}

Patent Claims

1. Use of thiazolo-[2,3-a]-isoindole derivatives of the formula I



(I)

for the preparation of medicaments with anti-viral action, whereby X can be an oxygen or sulphur atom, the imino group =NH or an N-C_1-C_5-alkylimino group, n is equal to 0, 1 or 2, R signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 9 C-atoms, which can be substituted by phenyl, or a C_1-C_6-alkoxy-C_1-C_6-alkyl or C_1-C_6-alkylmercapto-C_1-C_6-alkyl radical or signifies a phenyl ring which is possibly substituted one or more times by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_2-C_6- alkenyl, C_2-C_6-alkynyl, C_2-C_6-alkenyloxy, C_2-C_6-alkenylmercapto, C_2-C_6-alkynyloxy, C_2-C_6-alkynylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylcarbonyl-amino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, aminocarbonyl, hydroxyl, benzyloxy, phenylmercapto, phenyloxy, nitro, cyano, halogen, trifluoromethyl,

azido, formylamino, carboxyl or phenyl or signifies a mono-, bi- or tricyclic carbocyclic ring with 7 - 15 C-atoms or a heterocyclic mono-, bi- or tricyclic ring system with, in each case, 5 or 6 ring atoms and, per ring system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, and these rings can be substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy, nitro, amino or halogen, R^1 signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 6 C-atoms or C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, carboxyl, halogen, hydroxyl, nitro, cyano, azido, phenyl or benzyloxy, R^2 has the same meaning as R^1, whereby the radicals R^1 and R^2, independently of one another, can be the same or different, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, morpholinocarbonyl, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aryloxycarbonyl, hetaryloxycarbonyl, aryl-C_1-C_6-alkoxycarbonyl, hetaryl-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxy-C_1-C_6-alkoxycarbonyl or hydroxy-C_1-C_6-alkoxycarbonyl, whereby the aryl and hetaryl radicals can, in each case, be substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy or halogen and R^4, R^5,

R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as the tautomers, enantiomers, diastereomers and physiologically acceptable salts thereof, with the proviso that, for the case that R^1, R^2, R^3, R^4, R^5 and R^6 simultaneously signify hydrogen, n the numbers 0 or 1 and X an oxygen atom, the radical R cannot signify hydrogen, an aliphatic group with 1 - 7 C-atoms, which can be substituted by phenyl, or phenyl which is substituted one or more times by C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxyl, trifluoromethyl, methylsulphonyl or halogen.

2. Use according to claim 1, characterised in that R represents a carbocyclic ring with 7 - 15 C-atoms selected from the group naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indanyl, indenyl, acenaphthylenyl, norbornyl, adamantyl, C_3-C_7-cycloalkyl or C_5-C_8-cycloalkenyl.

3. Use according to claim 1, characterised in that R signifies a heterocyclic mono-, bi- or tricyclic 1-, 2- or 3-ring system with, in each case, 5 or 6 ring atoms and, per ring system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, selected from the group pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrrole, pyrazole, imidazole, triazole, thiazole, oxazole, isoxazole, oxadiazole, furazane, furan, thiophene, indole, quinoline, isoquinoline,

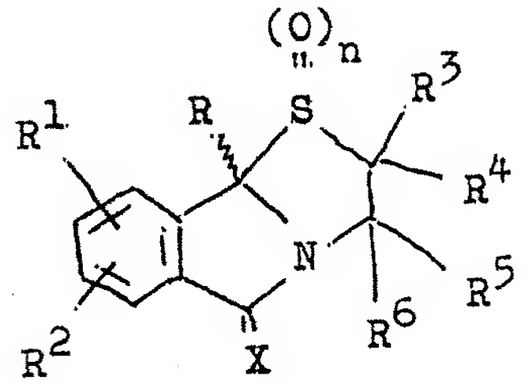
cumarone, thionaphthene, benzoxazole, benzthiazole, indazole, benzimidazole, benztriazole, chromene, phthalazine, quinazolline, quinoxaline, methylene-dioxybenzene, carbazole, acridine, phenoxazine, phenothiazine, phenazine or purine system, whereby the unsaturated or aromatic heterocycles can be partly or completely hydrogenated.

4. Use according to claim 1, 2 or 3, characterised in that R^1 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, sulphonamide, amino, hydroxyl or halogen and R^2 hydrogen or halogen.

5. Use according to one of claims 1 - 4, characterised in that R^3 and R^4 signify hydrogen.

6. Use according to one of claims 1 - 5, characterised in that R^5 signifies hydrogen, C_1-C_6-alkyl, carboxyl, C_1-C_6-alkoxycarbonyl, morpholinocarbonyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxy-C_1-C_6-alkoxycarbonyl, pyridyl-C_1-C_6-alkoxycarbonyl or halogen and R^6 hydrogen.

7. Thiazolo-[2,3-a]-isoindole derivatives of the general formula I



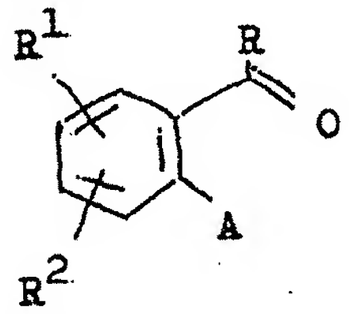
(I),

in which X can be a sulphur or oxygen atom, the imino group =NH or an N-C_1-C_5-alkylimino radical, n is equal to 0, 1 or 2, R signifies a heterocyclic mono-, bi- or tricyclic ring system with, in each case, 5 or 6 ring atoms and, per ring system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, and these rings can be substituted by C_1-C_6-alkyl, C_1-C_6-alkoxy, nitro, amino or halogen, R^1 signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 6 C-atoms or C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, carboxyl, halogen, hydroxyl, nitro, cyano, azido, phenyl or benzyloxy, R^2 has the same meaning as R^1, whereby the radicals R^1 and R^2, independently of one another, can be the same or different, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, morpholinocarbonyl, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aryloxycarbonyl, hetaryloxycarbonyl, aryl-C_1-C_6-alkoxycarbonyl, hetaryl-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxy-C_1-C_6-alkoxycarbonyl or hydroxyl-C_1-C_6-alkoxycarbonyl, whereby the aryl and hetaryl radicals can, in each case, be substituted by C_1-C_6-alkyl, C_1-C_6-

alkoxy or halogen, R^4, R^5, R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as their tautomers, enantiomers, diastereomers and physiologically acceptable salts.

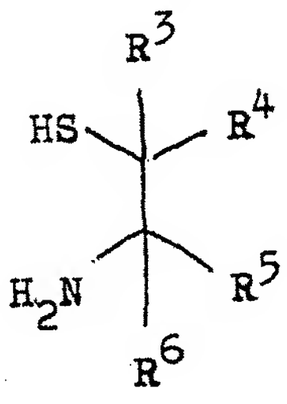
8. Thiazolo-/2,3-a/-isoindole derivatives according to claim 7, characterised in that R signifies a thienyl, furyl, pyridyl, thionaphthenyl or indolyl group possibly substituted by C_1-C_6-alkyl or halogen.

9. Process for the preparation of thiazolo-/2,3-a/-isoindole derivatives according to claims 7 or 8, characterised in that one reacts possibly substituted benzoic acid derivatives of the general formula II



(II)

in which R, R^1 and R^2 have the above-given meaning and A is equal to -COOH or C=N, with substituted or unsubstituted cysteamine of the general formula III



(III)

in which R^3, R^4, R^5 and R^6 have the above-given meaning, in a suitable inert solvent at room

temperature to reflux temperature, possibly in the presence of catalytic amounts of acids, isolates compounds of the formula I and possubly reacts compounds of the formula I to other compounds of the formula I and possibly separates the racemates obtained into their optically-active forms.

10. Medicaments containing at least one compound of the formula I according to one of claims 7 or 8.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente